Medical Progress

Short Stature—Physiology and Pathology

DAVID L. RIMOIN, MD, PhD, *Los Angeles;* ZVI BOROCHOWITZ, MD, *Torrance, California, and* WILLIAM A. HORTON, MD, *Houston*

Stature, the quantitative measure of height, varies widely within each ethnic group with a fairly normal distribution. Of the numerous patients whom physicians encounter because of short stature, relatively few are pathologically small in the context of family and ethnic background. Physicians must be able to differentiate pathologic short stature from the lower end of the normal curve before embarking on a complex diagnostic evaluation. There are literally hundreds of different causes of short stature, and the clinical evaluation requires a wide variety of clinical, radiographic, pathologic and biochemical tools. Although specific treatment to promote growth is available only in persons with the endocrinopathies and the acquired nutritional, emotional and chronic disease states, diagnosis of the specific form of short stature can have great importance in being able to prevent complications and to offer accurate prognostic information and genetic counseling.

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Normal stature varies widely among ethnic groups and varies within each ethnic group in a fairly normal distribution. "Short stature" is therefore an imprecise term and clearly relative to a person's ethnic, familial and nutritional background. Relatively few of the many patients who complain of short stature are pathologically small. Thus, it is imperative that before beginning a complex diagnostic evaluation or contemplating growth-promoting therapy, physicians are able to differentiate between pathologic short stature and the lower end of the normal curve. This will become even more important as unlimited supplies of human growth hormone become available through recombinant DNA technology. Regardless of its cause, however, short stature can result in psychosocial problems that are fairly independent of the relative degree of growth retardation. A physician must therefore take a patient's complaint seriously, confirm whether or not a pathologic form of short stature exists and decide on the appropriate therapy and counseling.

Normal Growth

The normal growth curve has characteristics that are shared by different ethnic groups, the mean and range of height varying among populations (Figure 1).[1,2] It is characterized by rapid fetal growth, with the peak intrauterine growth velocity occurring at about the fourth month of gestation.[2] There is quick deceleration of growth following birth, a period of relatively slow but constant growth during childhood, a rapid growth spurt at puberty and total cessation of growth with epiphyseal fusion. A person's growth potential is felt to be determined primarily by genetic factors through the combined effects of many genes (polygenic inheritance) and is thus similar to that of the birth parents.[3] Differences in height between normal persons are due to the interaction of this polygenic growth potential with environmental factors, such as nutritional deficiency or chronic disease.

Size at birth is thought to be highly correlated with intrauterine environment as well as genetic factors. The maternal environment and genotype have long been considered far more important than fetal genotype in determining birth size. Recent studies, however, have suggested that intrinsic fetal factors may be more important than previously considered. Nevertheless, between birth and 2 years of age, infants make adjustment for those maternal factors that influence birth length and increase or decrease their growth velocity in relationship to the norm to reach their genetic potential.[4] A person's height at 2 years of age is highly correlated with final adult height. Between birth and 2 years of age, the growth rate continues to decrease and levels off at between 2 or 3 years until rapid growth occurs at puberty (pubertal growth spurt). During childhood, significant alterations in body pro-

From the Division of Medical Genetics, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, California, and the Department of Pediatrics, University of Texas Medical School at Houston. Dr Rimoin is now with Cedars-Sinai Medical Center, Los Angeles.

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Reprint requests to David L. Rimoin, MD, PhD, Director, Department of Pediatrics, and Director, Medical Genetics—Birth Defects Center, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
GHRF = growth hormone-releasing factor
hCS = human chorionic somatomammotropin
hGH = human growth hormone
hGH-N = human growth hormone, normal (active)
hGH-V = human growth hormone, variant (inactive)
Ig = immunoglobulin
IGF = insulinlike growth factor
IGHD = isolated growth hormone deficiency
MR = magnetic resonance
U/L = upper segment length v lower segment length

portions take place with rapid growth of the limbs, so that the midpoint of the body changes from close to the umbilicus at birth to the symphysis pubis before the time of puberty.

Puberty is accompanied by a rapid increase in growth velocity, known as "the pubertal growth spurt." Before puberty, male and female children are remarkably similar in their height and growth velocities. In girls, the growth spurt occurs relatively early in the sequence of pubertal events, whereas in boys it occurs later. Thus, although the average boy enters puberty only six to eight months later than the average girl, his growth spurt occurs about two years later and lasts longer. In addition to the later and longer pubertal growth spurt in boys, the mean peak velocity is also greater. There is also a great deal of individual variation in the age of the onset of puberty, which also has a familial tendency. Persons who undergo puberty early are frequently taller than their peers at age 10 to 12 years, but growth ceases soon after puberty and their relatively short peers with late onset of puberty may surpass them in final adult height. In girls, menarche serves as a marker that growth is nearing an end. An average girl gains about 6 cm (2½ in) in height after menarche, but there is no such marker in boys.[1] The peak of the growth velocity in a boy may occur after he has become relatively sexually mature and he can still grow for several years thereafter (Figure 1). In addition to absolute height during the growth period, skeletal maturity is an important index of growth. Skeletal maturity is measured by the relative radiographic appearance of the epiphyses and metaphyses but reflects the overall biologic maturation of each person and is related to the relative age of the onset of puberty. Girls generally mature faster than boys, but the rate of maturation varies widely and appears to be genetically determined. Some children may take 14 years to reach final adult height, while others may require 20 or more years. Thus, height at a particular age is determined not only by one's genetic growth potential (which determines final adult height) but also by the degree of skeletal maturation (which is related to the age one achieves final adult height). For example, "tall for age" children may be so either because they have average growth potential but are more mature than their peers or because they have the genetic potential to be tall and are of average maturity. Factors that delay skeletal growth such as chronic illness, malnutrition and so forth usually also delay skeletal maturation. Dental maturation parallels osseous maturation and, thus, estimation of the dental age by tooth formation and eruption may be another index of skeletal maturation. In general, however, skeletal age is better evaluated by bone maturation than by tooth formation, as the correlation between tooth formation and body growth is not as well established.

Each normal person thus follows a growth curve that is accompanied by orderly and well-correlated changes in body proportions, dental eruption and epiphyseal ossification. All of these depend primarily on the person's genetic constitution but may be altered, either permanently or transiently, by influences such as nutrition and disease.

Measures of Growth

To judge whether a child has normal growth and maturation, standard normal curves are required. Such curves have been developed both for absolute accumulated height, the so-called distance curves, and for growth velocity.[5,6] Because there are great differences in growth rates, adult height and age of onset of puberty among different ethnic groups, it would be of great advantage to use standards based on ethnic background for each person assessed. Unfortunately, such curves are generally not available. Thus, in using these growth curves for nonwhites, adjustments should be made for ethnicity, especially in those groups such as southeast Asians whose mean height differs significantly from that of whites.

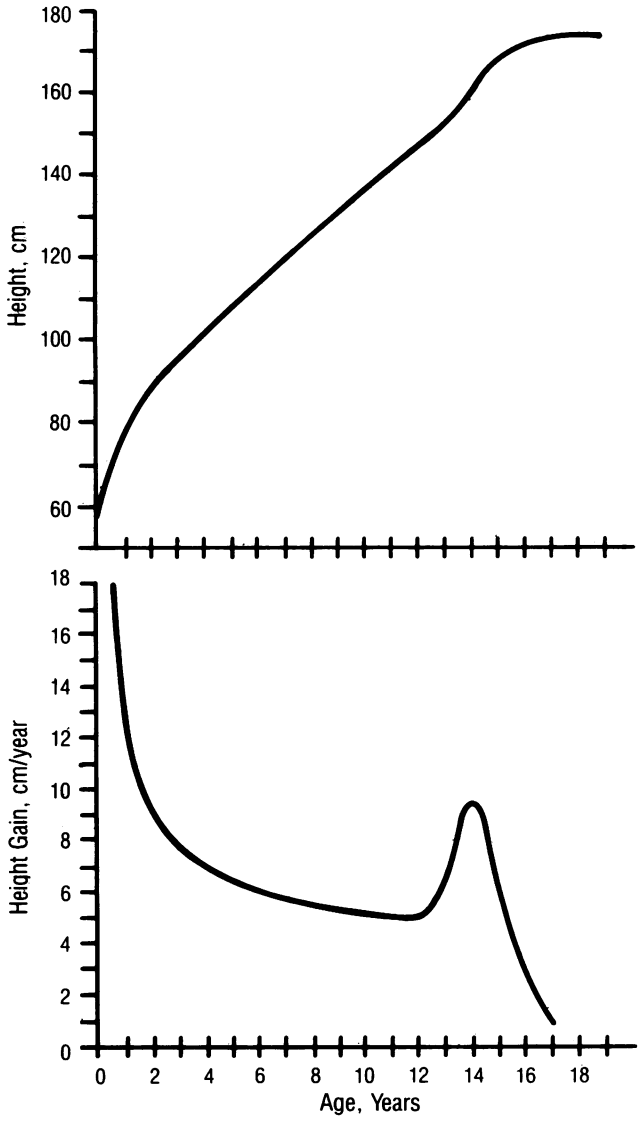

Figure 1.—Idealized normal growth curve: The top graph shows accumulated height and the bottom shows growth velocity.

An adjustment should also be made for children of lower socioeconomic backgrounds and disadvantaged countries who are more apt to have nutritional deficiencies and chronic infectious diseases, which tend to limit the ability to reach genetic height potential. Moreover, growth curves allowing for parental height correlations can also be used, especially if the parents' heights fall at either end of the normal spectrum.[7]

The usual growth curves are divided into percentiles around an arithmetic mean. Although the 97th and 3rd percentiles are usually taken as the upper and lower limits of normal, it must be emphasized that, by definition, 3% of normal children lie beyond both the 3rd and 97th percentiles. Because there is a correlation between a child's height and parental stature, adjusting for parental height can add accuracy. For example, a child with short parents who falls at the 3rd percentile for height might be considered abnormally short, but if midparental height is considered, the child's corrected height is well within normal limits.

After the age of 2 years, there is a tendency for each child to follow the same percentile of the growth curve. Deviation may signal a pathologic process interfering with growth. A normal child may deviate from this percentile during adolescence, depending on the timing of the pubertal growth spurt. Growth-curve data can also be used to calculate "height age." The height age is defined as the age at which a child's height would fall at the 50th percentile. Although this measurement may be slightly inaccurate because it assumes that all persons grow at the 50th percentile, calculations of height age are useful in correlating the stature of a person with the degree of skeletal maturation.

Growth-velocity curves are more accurate in following the progress of an individual child's growth. Growth-velocity determinations should, however, be made over relatively long intervals—that is, six months or a year—because normal persons fluctuate widely in their short-term growth velocities (Figure 1).

A variety of standards have been developed to assess maturity.[8,9] Skeletal maturity serves as a good index of overall biologic maturation and correlates well with other variables, such as dental maturity and onset of puberty. Skeletal maturity is based on the size and shape of the epiphyses on x-ray films. Although a number of areas of the body have been used to evaluate this process, the hand and wrist provide a large number of bones to examine and are the most convenient for general use. With the Greulich-Pyle method, a hand x-ray film of the child in question is compared with a set of standard hand films at different ages; that age standard that most closely resembles the child's films is given as the bone age. Different standards must be used for boys and girls because of differences in the rate of maturation. More accurate and time-consuming methods for assessing bone age have been developed, such as the TW2 system, that are based on the radiographic appearance of several epiphyseal sites.[9]

Various standards have been developed for anthropometric measurements of body proportions. The upper/lower segment (U/L) ratio is an easily obtained and useful index of body proportion (Figure 2). The lower segment is measured from the symphysis pubis to the floor at the inside of the heel. The upper segment figure is obtained by subtracting that of the lower segment from the total height. Standard U/L ratio curves have been published for both white and black Americans.[10] For example, a white infant has a U/L ratio of about 1.7; it reaches 1.0 at 7 to 10 years and falls to a mean of 0.95 in adulthood. Blacks have relatively long limbs and reach a U/L ratio of about 0.85 as adults. Although standard curves are not available for people of Asian and American Indian background, they appear to have relatively shorter limbs and therefore would be expected to have a somewhat higher mean U/L ratio than whites. Arm-span measurements are another index of body proportion, as the arm span usually falls within a few centimeters of the total height. For example, short-trunked dwarfs will have a low U/L ratio and an arm span considerably greater than their height. Sitting height is a more accurate measure of body proportion but is more difficult to use in a standard office practice.

Physiology of Growth

Growth is a product of continuous interaction between the endocrine and skeletal systems. Nearly all of the body's hormones influence growth.[11,12] For example, growth hormone, thyroxine, insulin and corticosteroids can all affect growth rate, whereas parathormone, 1,25-dihydroxyvitamin D and calcitonin all modulate skeletal mineralization and development. In addition, gonadal and adrenal steroids are of primary importance in skeletal maturation and the pubertal growth spurt.

The key factor in this growth regulatory scheme is the human growth hormone (hGH). This relatively small peptide hormone (191 amino acids) is made by specific cells (somatotropes) in the anterior pituitary gland. hGH is coded for by a gene that has been mapped to the distal end of the long arm of chromosome 17 (17q).[13] Differential messenger RNA splicing results in two populations of hGH molecules (20K and 22K). In addition to the gene coding for active hGH (hGH-N), this gene cluster also contains an apparently inactive hGH-like gene (hGH-V), genes coding for human chorionic somatomammotropin (hCS, also known as placental

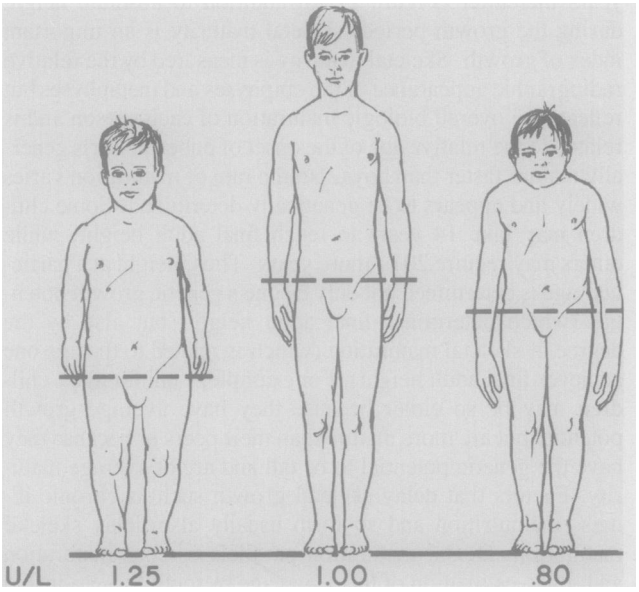

Figure 2.—Disproportionate short stature: compared with a normal 8-year-old child in the center, the child on the left has short limbs and short stature with an elevated U/L ratio, whereas the child on the right has a short trunk and short stature with a reduced U/L. U/L = upper segment length versus lower segment length.

lactogen) together with a number of related genes that do not code for well-known hormones. To date, five nonallelic hGH or hCS genes in this cluster have been cloned and sequenced.[14,15]

Pituitary hGH secretion is primarily regulated by two hypothalamic hormones: growth hormone-releasing factor (GHRF) and somatostatin.[16] Growth hormone secretion is stimulated primarily by hypothalamic GHRF in a pulsatile manner, the maximum pulse occurring at the onset of slow-wave sleep. Growth hormone secretion is regulated by means of a series of negative feedback loops involving the somatomedins and growth hormone itself operating via the regulation of the relative release of the two hypothalamic hormones. The synthesis and release of hGH in the somatotropes is under the control of the adenosine 3′:5′-cyclic monophosphate system. After growth hormone is released into the circulation, its major growth-stimulating effects are modulated through the stimulation of the production of the somatomedins in the liver.[17]

The somatomedins, which are more commonly referred to now as the insulinlike growth factors (IGF), comprise two major types: insulinlike growth factor I (IGF I), which is identical to somatomedin-C, and insulinlike growth factor II (IGF II).[17–19] These growth factors, which are homologues of proinsulin, have biologic effects qualitatively similar to insulin. These molecules weigh about 7,500 daltons and share about 50% of the amino acids of the insulin molecule. Radioimmunoassays for each of these IGFs have been developed and the genes coding for them have been mapped to chromosomes 11 and 12. Production of both IGF I and IGF II appears to be under hGH control. Although the results of recent studies suggest a direct effect on longitudinal growth by hGH itself, the bulk of evidence suggests that the major mechanism through which hGH stimulates bone growth is via the production of IGF I.[20,21]

Skeletal maturation appears to be under the primary control of hormones from the thyroid, adrenal and sex glands. An excess of any one of these will accelerate bone maturation, whereas a deficiency will cause delay. At puberty, both the sex hormones and growth hormone participate in producing the pubertal growth spurt; the ceasing of growth that follows this spurt is due primarily to the action of the sex hormones in closing the epiphyses.

The skeleton responds to these stimuli by two major forms of ossification—endochondral and membranous. In endochondral ossification, the precursor for bone is formed as cartilage. The development and subsequent growth of those bones result from the transformation of this cartilage into true bone. Endochondral ossification is largely responsible for the elongation of individual bones and is thus the major process contributing to the increase in height, or "growth." With membranous ossification, the bone is directly formed from the membrane that surrounds the bone (periosteum). There is no cartilage intermediary. This process occurs primarily in the calvarium, the clavicles and parts of the jaw, spine and pelvic bones. In addition, the widening of limb bones results from this process. Thus, an increase in the length of a bone is due to endochondral ossification, whereas an increase in its width is due to membranous ossification.[12]

Endochondral ossification commences at seven weeks of fetal life when primitive mesenchymal tissue forms cartilage in areas destined to become bone. Within two weeks, blood vessels penetrate into the center of the bone-to-be and the ossification process has begun. The transformation spreads rapidly, so that, by three months, most of the precursor has been converted into true bone. Cartilage is retained only at the ends of the bones, where it continues to grow and be converted into bone. This site, which is similar in all long bones, is termed the endochondral growth plate. Microscopically it can be seen as a very orderly region composed of distinct zones of cartilage cells synchronously proliferating, maturing, degenerating and finally dying as the cartilage is replaced by bone. Several of the hormones mentioned previously, especially IGF I, to which the chondrocytes possess specific receptors, are thought to regulate this process.[12] After puberty, the growth plate disappears, all remaining cartilage is replaced by bone and skeletal growth ceases.

Differential Diagnosis of Growth Retardation

The first step in evaluating for short stature is to determine if it is pathologic. This can be done by using standard growth curves with adjustments for ethnic and family background and by determining the skeletal maturity of prepubertal persons. The most common causes for complaints of short stature that physicians encounter are not pathologic but fall within the range of normal human variability—that is, familial short stature and constitutional delay.

Familial Short Stature

The normal variation in stature in each population is thought to be polygenic in nature, due to the interaction of many genes and environmental factors. The normal growth curves have been derived by measuring large numbers of normal children at different ages and plotting the mean and range of their heights. Depending on the particular curve, either the 5th or the 3rd percentile are frequently taken as the "lower limit of normal," even though it is clearly recognized that 5% or 3%, respectively, of the normal population fall below this level. These people are frequently considered to be abnormally short, although it is only the minority of persons falling below the 5th percentile who are truly pathologically short. Most persons who fall at the low end of the normal curve have familial short stature because they are genetically programmed to be short—that is, they are children of short parents and are growing appropriately for their genetic endowment. Their skeletal maturation (bone age) is commensurate with chronologic age and they are otherwise completely healthy.[2,12]

It is thus important that parental height be considered when evaluating short persons because this is generally the best indicator of their polygenic makeup and can be used to predict expected height. For instance, consider an otherwise healthy and normally proportioned child growing at the 3rd percentile with a bone age consistent with the chronologic age (height age is significantly younger than bone age). If the parents are relatively tall, this child might be considered to have significant growth delay, but if the midparental height (mean of the parents' height) is at the 3rd percentile, the child's growth is appropriate for his or her genetic constitution and the diagnosis of familial short stature can be made. Methods are available by which the midparental height measurement can be used to adjust a child's position on standard

growth curves and thus compensate for short parental height.[7] This may not be necessary, however, as a simple mental adjustment will usually suffice. Once a diagnosis of familial short stature is made, one must assure the child and the parents that the growth pattern is completely normal for his or her familial and ethnic background and that nothing can presently be done to safely stimulate the child's growth.

Constitutional Delay

Perhaps the second most common cause of referral for short stature is known as constitutional delay or constitutional slow maturation.[2] Such children are normal but are small for their age and have sexual and skeletal maturation that is commensurately delayed—that is, their height and bone ages are equally delayed. These persons can be expected to undergo puberty at a relatively late age, but they have a normal pubertal growth spurt and reach the normal adult range for stature. Constitutional growth delay, therefore, represents the lower end of the normal range of timing of skeletal and pubertal development. These children are simply programmed to take longer than average to become sexually mature adults. Slow maturation is observed more frequently in boys, and a similar history is often found in their parents.[1] In most cases, treatment should be limited to reassurance that the child will develop normally. Providing a predicted adult height is quite useful, stressing that the child may eventually be taller than many of his earlier maturing, taller friends.[7,8] In those few persons in whom psychological problems exist, stimulating growth with the use of testosterone or oxandrolone may be indicated, with the proviso that eventual adult height will probably not be greater and may even be less than if nature were allowed to take its course. Clinical trials with recombinant DNA-derived growth hormone are presently under way in such patients.

Pathologic Short Stature

When a physician establishes that a person is truly short for his or her genetic background and does not simply have constitutional delay, the exact cause of the pathologic short stature must be delineated. It is essential that a specific diagnosis be made, if possible, because there are literally hundreds of causes of short stature that have different prognoses, complications and potential for treatment (Figure 3). The first step in the clinical evaluation of short stature is to determine whether the body habitus is proportionate or disproportionate (Figure 3). In general, children with disproportionate short stature have a skeletal dysplasia, whereas those with proportionate short stature usually have a more generalized disorder such as intrauterine growth retardation, malnutrition, chronic disease, psychosocial dwarfism, chromosomal anomalies or an endocrine disorder. Exceptions to this rule do occur, however, such as disproportionate dwarfism in cases of severe cretinism or the proportionate shortening that may occur in persons with osteogenesis imperfecta. A mildly disproportionate body habitus may not be apparent on casual examination and, thus, anthropometric measurements, such as sitting height or upper/lower segment ratio and arm span must be made before a skeletal dysplasia, such as hypochondroplasia, can be excluded. Because of the differential growth of the trunk and limbs through childhood, normal body proportions vary with age and anthropometric measurements must be compared with appropriate standards for age. Once the stature of a short person is found to be proportionate, it is helpful to determine whether the growth was retarded prenatally or postnatally. A prenatal onset of growth retardation usually implicates a fetal environmental insult or a generalized cellular genetic defect. A postnatal onset of proportionate growth retardation, on the other hand, usually implicates a postnatal environmental insult, such as infection, chronic disease or malnutrition or an endocrine, psychological or malabsorption disorder.

Proportionate Short Stature of Prenatal Onset

Intrauterine Growth Retardation

When the onset of short stature is prenatal, one must differentiate between the various forms of intrauterine growth retardation. This is a very heterogeneous group of disorders with multiple causes ranging from placental insufficiency to teratogenic exposure to specific genetic or chromosomal syndromes. Although in most cases the cause is obscure, often a recognizable syndrome and a specific diagnosis can be made.[12,22] For example, Bloom's syndrome, Seckel's syndrome, Donahue's syndrome and Dubowitz's syndrome are all autosomal recessive disorders. On the other hand, the

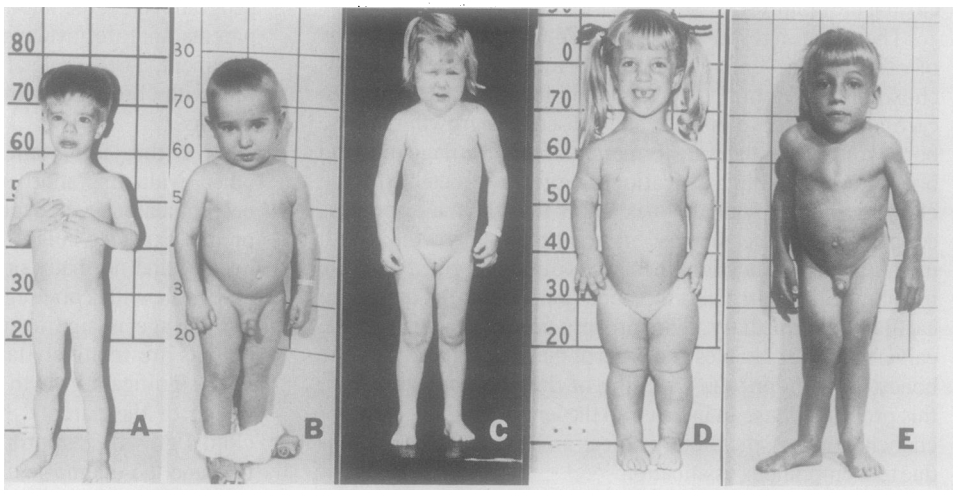

Figure 3.—Children of approximately the same age (5 to 7 years) with several forms of short stature (scale in centimeters): **A,** Bloom's syndrome. Autosomal recessive, associated with intrauterine growth retardation, proportionate short stature, photosensitive rash and predisposition to leukemia. **B,** Psychosocial dwarfism. Note the proportionate short stature, young appearance and protruding abdomen. **C,** Multitropic pituitary hormone deficiency. Note the youthful appearance and proportionate short stature similar to patient B. **D,** Achondroplasia. Note the short limbs with the arms extending only to the hip level and the peculiar facies with scooped-out bridge of the nose. **E,** Spondyloepiphyseal dysplasia with a short trunk. Note the normal head and short neck (from Rimoin and Horton[12]).

Hallermann-Streiff syndrome, Russell-Silver's syndrome, de Lange's syndrome and Williams' syndrome* usually occur sporadically and may represent new dominant mutations. Each of these syndromes has its own clinical and radiographic features that permit a diagnosis to be made or at least suspected. Establishing a diagnosis makes it possible for one to provide an accurate prognosis and genetic counseling.

Chromosomal Disorders

Most chromosomal disorders, with the exception of the multiple X and Y syndromes, result in intrauterine growth retardation. In addition to the prenatal growth retardation, those syndromes compatible with survival beyond infancy, such as trisomy 21, the X deletion syndromes (Turner's syndrome) and a variety of autosomal partial deletion and duplication syndromes, are characterized by continued poor growth throughout childhood and a blunted pubertal growth spurt as well. As the number of recognized chromosomal disorders has increased due to improved banding techniques, their precise clinical diagnosis has become increasingly difficult. Therefore, a patient with intrauterine growth retardation and dysmorphic features who does not fit into a recognizable syndrome should have karyotyping done to exclude a chromosomal anomaly. It should also be remembered that some girls with the Turner syndrome, especially those with mosaicism—that is, 45X, 46XX—may express few phenotypic features of this syndrome prepubertally, except for short stature. Thus, chromosomal studies should be done on all short girls with relatively normal body proportions for whom another diagnosis has not been made.

Intrauterine Infections

Intrauterine infections with rubella, syphilis, toxoplasmosis and cytomegalic inclusion disease can produce prenatal growth retardation that results in postnatal proportionate short stature.

Affected neonates are usually severely ill with systemic manifestations, including microcephaly, hepatosplenomegaly, petechiae and seizures. The diagnosis is ultimately made by determining elevated serum Torchs titers.

Teratogenesis

Maternal consumption of ethanol, nicotine, hydantoins and warfarin may result in prenatal growth retardation.[22] Maternal smoking may result in otherwise normal, small-for-dates babies, whereas the use of ethanol, hydantoins and warfarin produces well-characterized teratogenic syndromes.

Proportionate Short Stature of Postnatal Onset

Persons with a postnatal onset of proportionate short stature usually have a prenatal environmental insult, a chronic disease or an endocrine disorder, all of which may be associated with the insufficient generation of IGF or peripheral unresponsiveness to its action. There may be direct suppression of hepatic IGF synthesis, deficient hGH secretion with secondarily reduced IGF production, inability to respond to hGH stimulation of IGF, circulating IGF inhibitors and peripheral unresponsiveness to the actions of IGF. These children usually have a bone age commensurately or even more severely retarded than their height age, depending on the state of their gonadal and thyroid systems. An accurate diagnosis is especially important for persons with this group of disorders because many of them will respond to specific therapeutic measures.

Psychosocial Dwarfism

Emotional disturbances may result in pronounced growth retardation in certain children.[23] These children usually come from homes where marital discord, separation, promiscuity, alcoholism and the like are found, but they can also be seen in superficially well-to-do and well-adjusted families. A history of emotional deprivation may be readily apparent but in some children may be difficult to obtain. They usually have normal-growing sibs. There is usually a poor plasma hGH response to the usual stimuli and levels of circulating IGF are low. Other pituitary hormone deficiencies can also be found. Bone-age maturation is usually greatly delayed. When removed from their adverse environment, these children show a striking catch-up in their bone age and their hGH and IGF levels return to normal. Psychosocial dwarfism is thought to represent functional hypopituitarism in which psychic factors have produced pituitary insufficiency through hypothalamic suppression. This condition appears to be relatively common but it usually occurs in only one person in a family.

Malnutrition

Chronic malnutrition retards growth and is associated with reduced synthesis of IGF.[18] Indeed, children with protein-calorie malnutrition (kwashiorkor) have low serum IGF despite high levels of hGH. While caloric intake appears to regulate IGF generation, dietary protein seems to be important in both maintaining IGF activity and influencing the IGF action at the tissue level. The absence of an adequate substrate for growth may contribute to growth failure in malnutrition as well. Malnutrition resulting from malabsorption may also result in growth retardation. There have now been several reports of cases of otherwise asymptomatic celiac disease resulting in persons with proportionate growth retardation.[11] Small bowel biopsies have been recommended in the workup for such children in whom other causes of growth retardation have been excluded.

Chronic Disease

Many chronic diseases of childhood are associated with growth failure.[11,12,24,25] Chronic liver disease, chronic renal disease, chronic celiac disease, regional enteritis, chronic infectious disease, diabetes mellitus, the hemoglobinopathies, asthma, congenital heart disease and many others fit into this category. Often the reduced growth may be the dominant clinical feature. Although the mechanism for growth suppression is varied, a low IGF level is usually found. In addition, many patients with chronic disease are in a state of negative nitrogen balance. Poor absorption of nutrients may be found in patients with gastrointestinal disorders such as regional ileitis. After cure or control of the disease, there is usually significant catch-up growth, the final adult stature depending on the duration and severity of the disease and the age of onset of the disorder and its therapy.

*Although eponyms are not written as possessives in the field of genetics, *WJM*'s style follows *Dorland's Medical Dictionary* (26th edition) and the AMA's *Manual for Authors and Editors*.

Drug Administration

In addition to the various intrinsic causes of reduced human growth hormone secretion, certain medications used in treating hyperactivity, such as methylphenidate (Ritalin) hydrochloride and dextroamphetamine, may alter the normal regulation of hGH secretion.[26,27] Children often show a lower-than-expected growth rate during the first few years after treatment is begun, but tolerance to the growth suppression seems to develop in many after several years. Similarly, glucocorticoids used in treating certain diseases such as asthma, the nephrotic syndrome, juvenile rheumatoid arthritis and leukemia may significantly retard growth. The growth-suppressing effects of steroids may be seen with relatively small doses that are often thought to be harmless—that is, the prolonged use of topical ointments, nasal spray or eye drops containing these compounds.[25] The long-term effects of these and other drugs on growth and final adult height have not been established.

Endocrine Disorders

Many disturbances in the endocrine system can impair growth.[12,24,28,29] Thyroid hormone deficiency can result in either proportionate or disproportionate short stature, depending on the degree of secondary epiphyseal dysplasia. Cushing's disease can lead to proportionate short stature similar to that seen with the exogenous administration of steroids. Excess gonadal steroid secretion or the adrenogenital syndrome can lead to accelerating growth with advanced bone age in early childhood, but significant adult short stature results due to premature closure of the epiphyses.

The prototype of endocrine short stature, of course, is hGH deficiency. Growth hormone-related causes of short stature can result from many interruptions in the hypothalamic or pituitary peripheral tissue axis. The various types of pituitary dwarfism can be classified on the basis of the level of the defect; whether it is genetic or acquired and, if genetic, the mode of inheritance; whether or not there is an obvious developmental or degenerative disease of the hypothalamus or pituitary; whether the pituitary deficiency is monotropic (isolated growth hormone deficiency) or multitropic, and, in those cases due to a defect in growth hormone action, whether somatomedin generation is normal or defective.

Acquired Pituitary Insufficiency

The most common causes of acquired prepubertal pituitary insufficiency are birth trauma, cranial irradiation for neoplasia, craniopharyngioma in which the expanding tumor mass compromises pituitary function and hemosiderosis following chronic transfusion therapy. In addition, trauma, surgical damage, infection and sarcoidosis can also lead to pituitary insufficiency.[12]

Developmental Anomalies Associated With Pituitary Insufficiency

A number of developmental anomalies of the hypothalamus and pituitary result in hGH deficiency with or without other tropic hormone deficiencies (Table 1).[29] Many of these syndromes are associated with facial or optic anomalies. In certain disorders, such as congenital absence of the pituitary, empty sella syndrome, transsphenoidal encephalocele and two rare syndromes associated with an unusually shaped or large sella turcica, lateral x-ray films of the skull may be sufficient to detect an intracranial anomaly. In other disorders, however, such as the holoprosencephaly syndromes and septooptic dysplasia, computed tomography (CT) or magnetic resonance (MR) imaging of the brain and hypothalamus may be necessary to detect the malformation. Thus, any hGH-deficient child with malformations of the face or eyes should have CT or MR imaging of the brain and sella turcica to rule out a malformation of the hypothalamus or pituitary gland.

Genetic Syndromes Associated With Pituitary Insufficiency

There are a number of genetic syndromes, unassociated with known developmental malformations of the hypothalamus or pituitary, that have pituitary insufficiency as a common component (Table 2).[29] In certain of these disorders, such as histiocytosis X and hemochromatosis, the hormonal deficiencies have been found to be due to degenerative disease of the hypothalamus and pituitary. In most of these syndromes, however, the pathogenesis of the pituitary insufficiency is unknown. Both sickle cell anemia and thalassemia are associated with delayed growth and sexual development with resultant adult short stature. In the thalassemias, this is apparently due to posttransfusion therapy resulting in hemosiderosis affecting the pituitary, whereas in persons with sickle cell anemia the exact cause of the short stature is unknown.

Idiopathic Hypopituitarism

The commonest form of growth hormone deficiency is the "idiopathic type"—that is, one in which no organic lesion can be found. This is a heterogeneous group of disorders, however, that can be classified on the basis of whether only growth hormone is deficient or whether there are multitropic

TABLE 1.—*Developmental Anomalies and Genetic Syndromes Associated With Hypopituitarism*

Congenital absence of the pituitary
Pituitary dwarfism with abnormal sella
Familial hypopituitarism with large sella
Empty sella syndrome
Anencephaly
Holoprosencephaly
Transsphenoidal encephalocele
Septooptic dysplasia
Cleft lip and palate with pituitary insufficiency
Solitary central maxillary incisor
Rieger's syndrome (iris-dental dysplasia)
CHARGE association (coloboma, heart disease, atresia choanae, retarded growth and/or central nervous system anomalies, genital anomalies and ear anomalies and/or deafness)
Orocraniodigital syndrome
Histiocytosis X
Hypothalamic hamartoblastoma-imperforate anus-polydactyly syndrome
Sensorineural deafness
Fanconi's anemia
Neurofibromatosis
Gonadal dysgenesis
Börjeson-Forssman-Lehmann syndrome
Aarskog's syndrome
Hemochromatosis
Hemoglobinopathies

TABLE 2.—*Genetic Forms of Pituitary Dwarfism*

Type	Isolated Growth Hormone Deficiency (IGHD)				Multiple Hormone Deficiency		Bio-inactive	Laron Dwarfism	IGF-I Resistance
	I-A	I-B	II	III	I	II			
Defect	Gene deletion	Hypothalamus	hGH	?	Hypothalamus or pituitary	?	hGH gene mutation?	hGH receptor	?IGF-I receptor
Inheritance	AR	AR	AD	X-linked	AR	X-linked	?	AR	?
Plasma									
GH	0	↓	↓	↓	↓	↓	N	↑	N/↑
IGF before/after hGH	↓/N	↓/N	↓/N	↓/N	↓/N	↓/N	↓/N	↓/↓	↑/↑
Insulin	↓	↓	↑	↓	↓	↓	↓	↓	↓
Response to GH treatment	±	+	+	+	+	+	−	−	−

AD = autosomal dominant, AR = autosomal recessive, GH = growth hormone, hGH = human growth hormone, IGF = insulinlike growth factor, N = normal, 0 = zero, ↓ = decreased, ↑ = increased, + = positive, − = negative (or none)

hormone deficiencies, whether it is genetic or acquired, and, if genetic, the mode of inheritance or whether the growth hormone molecule is normal or abnormal. In addition, these disorders must be distinguished from the various forms of IGF or growth hormone resistance. Perinatal problems such as breech or forceps deliveries, early vaginal bleeding, prolonged or unusually short labors frequently occur in persons with hypopituitarism, as do signs of intrapartum fetal distress or anoxia. It has been suggested that these perinatal insults lead to the hypopituitarism.

Multitropic Pituitary Hormone Deficiency

Multitropic pituitary hormone deficiency (panhypopituitary dwarfism) is associated with deficiency of hGH and one or more of the other pituitary tropic hormones. Although a great majority of the cases are sporadic and thought to be related to perinatal anoxia, at least two genetic forms of the disease have been described—autosomal recessive and X-linked recessive.[29] There is both interfamilial and intrafamilial variation in the associated hormonal deficiencies. In certain families, one person might lack all of the tropic hormones, whereas another may lack only hGH and gonadotropins. At least hGH and gonadotropin deficiency occur in all affected members, however. There have been no familial crossovers between multitropic pituitary hormone deficiency and isolated growth hormone deficiency yet reported. No clinical or endocrine differences exist between the two genetic forms of multitropic pituitary hormone deficiency and the more common acquired disease, making genetic counseling difficult in sporadic cases. The clinical features of this syndrome depend on which of the tropic hormones is deficient. The basic defect appears to lie at the hypothalamic, rather than the pituitary, level in about two thirds of the cases.

Isolated Growth Hormone Deficiencies

Isolated growth hormone deficiencies (IGHD) with otherwise normal pituitary function result in proportionate dwarfism with normal sexual development. Although most persons with hGH deficiency have a fairly typical physical appearance with characteristic metabolic abnormalities, it is now apparent that on the basis of clinical, genetic, molecular and metabolic variability, IGHD is a heterogeneous group of disorders.

IGHD type I. The most common form of IGHD, type I (also referred to as type I-B), is inherited as an autosomal recessive trait and is associated with proportionate dwarfism, increased subcutaneous fat, typical pinched face with high forehead, wrinkled skin and high-pitched voice.[29] Persons with this disorder may have spontaneous hypoglycemic episodes in infancy, but this is not a problem after early childhood, although they maintain hypersensitivity to exogenous insulin into adulthood. As adults, abnormal glucose tolerance associated with insulinopenia is characteristic. Puberty occurs spontaneously but is frequently delayed to the late teens or early twenties. Puberty frequently appears abruptly during the first months of hGH therapy, however. Growth hormone release has been documented following administration of growth hormone-releasing factor, and immunoultrastructural studies have shown normal hGH-staining granules in the pituitary gland of an affected person, suggesting that the basic defect in this disorder is at the hypothalamic, rather than the pituitary, level.[30] Furthermore, linkage studies using restriction fragment length polymorphisms of the growth hormone gene have shown a lack of linkage between the hGH gene and type I IGHD.[31]

IGHD type I-A. In 1971 Illig and co-workers described a type of growth hormone deficiency that was felt to be distinct from type I on the basis of a total lack of immunoactive hGH and the appearance of high concentrations of hGH antibodies following hGH therapy, rendering the subjects resistant to hGH therapy.[32] This syndrome was described in an inbred Swiss kindred and was felt to be inherited as an autosomal recessive trait. It was said to result in shortness at birth and even more severe dwarfism and exaggeratedly pinched faces than in the more common forms of hGH deficiency. During hGH therapy, however, hGH antibodies develop in high concentrations, which suppress its growth-promoting effects. Using restriction endonuclease analysis, Phillips and associates recently studied nuclear DNA from four cases originally reported by this Swiss group.[15] They found that the patients were homozygous for a deletion of at least 7.5 kilobases of DNA. This deletion included the gene that codes for normal hGH (hGH-N gene) but not the variant hGH (hGH-V) gene. They have recently reported the cases of three siblings from an Argentine family with an apparently identical hGH-N deletion who had some minor phenotypic differences from the Swiss families.[33] These differences included the fact that only one of the patients had intrauterine growth retardation whereas the others had normal birth weight and length. Furthermore, although hGH antibodies developed in all patients, growth persisted with hGH therapy in two of them. Phillips has recently found a number of other patients of Japanese, Italian, Austrian and Spanish backgrounds with type I-A IGHD.[34] These last patients had functionally identical dele-

tions of the hGH-N gene but, in contrast to the Swiss and Argentine patients, the deletions were each physically somewhat different from the other. Thus, type I-A IGHD appears to be a result of a deletion in the hGH gene, with a resultant congenital absence of normal hGH and a lack of immunotolerance to homologous hGH. This would explain the total absence of immunoreactive hGH and the patients' high antibody titers following hGH administration. It is of interest that a number of patients have now been described with various mutations or other deletions in the hGH gene cluster that spare the hGH-N gene. These patients have been of normal height and are otherwise clinically normal but had complete antenatal deficiency of hCS production. The sparing of the hGH-V gene in type I-A IGHD and its inclusion in the deletion in these families indicates that the hGH-V gene expression is not necessary for either prenatal or postnatal growth.

IGHD type II. IGHD type II was first defined as a distinct form of hGH deficiency that was associated with increased rather than decreased insulin response to glucose and arginine, apparently inherited as an autosomal dominant trait.[29] These persons do not seem to have the wrinkled skin or characteristic voice seen in other pituitary dwarfs. It is now clear that there is more heterogeneity in the IGHD syndromes than a simple division into type I and type II because there have been families reported with apparent dominant inheritance who have the metabolic features of the recessive form of the disease. On the other hand, persons who clinically resemble those with type I IGHD have been reported with familial aggregation, suggesting autosomal dominant inheritance. Results of preliminary linkage studies with restriction fragment length polymorphisms of the hGH gene have suggested that in cases of type II IGHD, it is the hGH gene itself that is involved. Phillips has postulated that a dominant disorder could be the result of a mutation in the signal peptide of the hGH gene affecting the intracellular transfer of the hormones.[34]

Pituitary Dwarfism With Biologically Inactive hGH

In 1978 several cases were described of patients with the clinical features of IGHD who achieved normal plasma immunoreactive hGH levels following stimulation but who had low levels of IGF.[35] Following hGH administration, however, they generated normal IGF levels and had a significant increase in their growth rates.[36] Pituitary function was otherwise normal. It was postulated that these persons secreted an abnormal growth hormone molecule that was biologically inactive but immunologically cross-reactive. Valenta and colleagues have recently reported the case of a patient who had normal levels of immunoreactive hormone with decreased radioreceptor-assayable and bioassayable activity.[37] This patient differed from the original patients noted above in that he had a normal plasma somatomedin level. When treated with an exogenous hGH, however, his response was excellent. Biochemical analysis of the patient's serum showed a structural abnormality of the circulating growth hormone, with most of the immunoactive growth hormone migrating as large molecules. The authors concluded that abnormal growth hormone structure should be suspected in children with short stature who have a normal serum growth hormone concentration, normal growth hormone response to the usual stimuli and normal pituitary function and who respond readily with linear growth to human growth hormone therapy. This raises the question as to which short children should have trials with hGH. The biologic activity of the circulating hormone in these patients is low, which can be established by determining the ratio of radioreceptor-assayable to radioimmunoassayable hormone or by bioassay. The authors point out that a low IGF concentration is not a diagnostic prerequisite of this type of pituitary dwarfism, as their patient had normal serum levels of IGF. It is likely that various other forms of pituitary dwarfism are associated with structural abnormalities in the growth hormone molecule. Phillips, however, could find no trace of a defect in the hGH-N gene following careful DNA analysis in such a patient.[34] He postulates that the hGH receptor in the liver may be involved, rather than the hGH gene. Some of these patients have had a deletion on chromosome 13 rather than on chromosome 17 on which the hGH gene is located. Further studies will be needed to document the defect in this disorder.

X-Linked Isolated Growth Hormone Deficiency and Hypogammaglobulinemia—IGHD Type III

A kindred has been described in which two brothers and their two maternal uncles had a syndrome consistent with hypogammaglobulinemia and isolated hGH deficiency.[38] They had proportionate short stature, retarded bone age in childhood, delayed onset of puberty, lack of plasma hGH response, low bioassayable and immunoassayable IGF and otherwise normal pituitary function. Recurrent pulmonary infections were a problem in two patients, which were abated by gammaglobulin therapy. Three of the patients had panhypogammaglobulinemia and an absence of circulating B cells, whereas the other patients had normal serum immunoglobulin (Ig) A and IgM levels and decreased levels of circulating B cells. T-cell function and number were normal. These patients appear to have a distinct X-linked recessive form of isolated hGH deficiency associated with hypogammaglobulinemia.

Partial Growth Hormone Deficiency

Several authors have described cases of short children with growth hormone responses above the usual cutoff point for growth hormone deficiency (7 ng per ml), who have either modest responses (less than 10 ng per ml), low IGF levels, decreased integrated growth hormone concentrations over a 24-hour period, a decreased number of hormone peaks or decreased responses following sleep. The common factor in these children was that they did not have growth hormone deficiency but seemed to respond to growth hormone therapy.[39] Furthermore, some of these children reverted to normal hGH responses to pharmacologic agents following either puberty or the administration of gonadal steroids. It is likely that there is a large number of patients with different forms of partial or transient growth hormone deficiency who may benefit from hGH therapy. An accurate description of these cases will be of great importance once unlimited supplies of growth hormone become available.

IGF Deficiency or Resistance

The various forms of true pituitary dwarfism are associated with diminished or absent secretion of growth hormone and a secondary deficiency of IGF. Various syndromes have been described in which growth hormone secretion is normal

or high and there is peripheral insensitivity to the effects of growth hormone administration; plasma IGF levels are low and responsive to growth hormone administration or elevated. Thus, these persons resemble pituitary dwarfs clinically but are resistant to the actions of growth hormone because they do not generate or respond to IGF.

Laron Dwarfism

Laron dwarfs clinically resemble patients with isolated hGH deficiency except for their normal or elevated growth hormone concentrations.[40,41] This autosomal recessive syndrome was first described in Asian Jews but has since been found in numerous other ethnic groups. These patients have the clinical appearance of patients with IGHD to an exaggerated extent, with severe growth retardation, severely pinched faces, high-pitched voices and, when male, small genitalia. Early development is generally slow, fontanelle closure is delayed and many have symptoms of hypoglycemia. Hands and feet are small and, like pituitary dwarfs, they are obese and the body proportions are childlike. Their teeth may be discolored, defective and crowded. Visual and motor coordination are poor and their IQ scores are towards the lower end of the normal range. Laron has found that their U/L ratios are more than 2 standard deviations above the mean, indicating that their limbs are relatively short. After puberty, their skin appears prematurely aged, like that of pituitary dwarfs. Similarly, skeletal age and timing of puberty are delayed. Glucose intolerance is present in association with symptoms of hypoglycemia and hypoinsulinemia, as in pituitary dwarfs. Plasma growth hormone levels, however, are elevated but suppress normally with glucose. Plasma IGF-I concentrations are low and do not increase following growth hormone administration. These patients are resistant to the growth-promoting effects of hGH administration.

Plasma growth hormone appears to be qualitatively normal on the basis of serial immunoassay dilutions, electrofocusing and molecular size distribution. Furthermore, substantial quantities of receptor-active hGH have been found by radioreceptor assay. Using an erythroid progenitor technique, Golde and co-workers found that there was a specific cellular resistance to hGH in Laron dwarfs.[42] Furthermore, it had been found that liver cell microsomes from these patients do not bind hGH normally, although insulin does bind normally. Thus, the pathogenetic mechanism in Laron dwarfism appears to involve a defect in IGF generation, which is probably due to a universal defect in growth hormone receptors.[40,42]

The African Pygmies

The African pygmies, who inhabit the rain forests of Africa, resemble pituitary dwarfs in size and skeletal proportions but do not have the truncal obesity, peculiar facies and wrinkled skin of pituitary dwarfs.[28,29] Following insulin-induced hypoglycemia and arginine infusion, hGH levels are normal, but like patients with type I IGHD, African pygmies have decreased insulin levels and are hypersensitive to the effects of exogenous insulin. They are completely unresponsive to the lipolytic, insulin-tropic and nitrogen-retaining properties of hGH, and in initial studies, bioassayable IGF levels were apparently normal. These results lead to the suggestion that the short stature of the pygmies is due to a peripheral unresponsiveness to IGF. Reexamination of these blood samples with the new IGF immunoassays, however, indicate that the pygmies have a primary deficiency of IGF I with normal IGF II.[43] Furthermore, IGF levels do not increase following growth hormone administration. Thus, short stature of the pygmies may well be due to a primary deficiency of IGF I. This is in contrast to Laron dwarfs who are unable to generate either IGF I or IGF II. A number of white patients with similar primary deficiencies of IGF I have been described, suggesting that persons who clinically and metabolically resemble pituitary dwarfs but who have normal levels of immunoassayable hGH should have their IGF levels and responsiveness to growth hormone carefully evaluated.

IGF-Resistant Dwarfism

Several patients with proportionate dwarfism have recently been described who have elevated IGF-I concentrations and normal or elevated levels of circulating hGH.[44] IGF levels were elevated regardless of whether they were assayed by bioassay, radioreceptor assay or radioimmunoassay. In a case described by Bierich and associates, bone age and dental eruption were delayed and hypoglycemia occurred during the patient's first year of life, similar to the case in pituitary dwarfs.[45] Cultured skin fibroblasts from this patient showed a 50% decrease in IGF binding, suggesting defective IGF-I receptors as the cause of the IGF resistance. Thus, resistance to IGF I appears to be a basic defect in these patients. Whether or not there is a difference between those patients with normal plasma hGH levels and those with elevated plasma growth hormone levels remains to be answered.

Disproportionate Short Stature

If a disproportionate body habitus is found on physical examination, then the patient most likely has a form of skeletal dysplasia. This is a heterogeneous group of inherited disorders of connective tissue in which the clinical features are usually dominated by dwarfism.[46] Well over 100 distinct disorders have now been recognized and it is important to make a specific diagnosis so that an accurate prognosis can be given and proper genetic counseling provided. Furthermore, each of these disorders is associated with a variety of skeletal or nonskeletal complications, or both, that an accurate diagnosis will allow one to anticipate, treat promptly or prevent.

The differential diagnosis of disproportionate dwarfism requires that various clinical observations be made. Was the shortening evident at birth or did it begin at a later date? (In some disorders, growth may be normal for several years. For instance, in the X-linked form of spondyloepiphyseal dysplasia tarda, growth retardation is not apparent until between 5 and 10 years of age.) Are the limbs relatively short compared with the trunk (short-limbed dwarfism) or is the trunk primarily affected (short-trunk dwarfism)? Most of these disorders can be clearly classified into one or the other forms of disproportion. However, relative body proportions may change with age in some disorders such as metatropic dysplasia in which the limbs are relatively short at birth; because of progressive kyphoscoliosis, such patients become short-trunked dwarfs during childhood. If a child has short-limbed dwarfism, are all of the segments of the limb equally shortened or does the shortening primarily affect the proximal (rhizomelic), middle (mesomelic) or distal (acromelic) seg-

ments? Is the disorder limited to the skeleton, or are there extraskeletal abnormalities such as ligamentous laxity, joint contractures, myopia, cleft palate, clubfoot or hearing loss? The presence or absence of these extraskeletal complications may be helpful in making a diagnosis.

The family history may also be helpful in arriving at a diagnosis. For example, if two dwarfed siblings are born to normal parents, then achondroplasia, which is an autosomal dominant trait, is unlikely, and one should suspect an autosomal recessive disorder. The answers to these clinical and genetic questions may be sufficient to make an accurate diagnosis or to limit the diagnosis to a relatively small number of disorders. For example, a large head with bulging forehead, midface hypoplasia, lumbar gibbus, rhizomelic shortening of the extremities and trident configuration of the fingers strongly suggest the diagnosis of achondroplasia. Similarly, short limbs, polydactyly, congenital heart disease and oral frenula indicate a diagnosis of chondroectodermal dysplasia. In most cases, however, further studies are required to make a diagnosis.

The next step is to obtain skeletal radiographs. A series of films including anteroposterior and lateral views of the skull and spine and anteroposterior views of the pelvis and extremities should be taken. Attention should be paid to the specific parts of the skeleton that are involved (spine, limbs, pelvis, skull) and, within each, where the abnormality is located (epiphysis, metaphysis, diaphysis or all three). Because the skeletal radiographic features in many of these disorders change with age, reviewing radiographs taken at different ages when possible is helpful. Moreover, the epiphyseal closure, which occurs after puberty, frequently obliterates the specific abnormalities that would have permitted a specific diagnosis to be made had the films been taken before puberty. Nevertheless, skeletal films are often sufficient to make the diagnosis. Indeed, the classification of these disorders has been based primarily on their radiographic features. In many instances, however, only the general type of dysplasia, such as a spondyloepiphyseal dysplasia, can be recognized, but the specific entity cannot be identified on radiographic grounds alone.

The microscopic evaluation of growth-plate cartilage and bone is becoming an integral part of evaluating for disproportionate short stature.[47] Specific histopathologic or ultrastructural alterations have been recognized in patients with certain types of skeletal dysplasia, by autopsy studies or by the examination of biopsy specimens obtained from the iliac crest, costochondral junction or tibial epiphysis. In certain of these disorders, such as thanatophoric dysplasia, the pathologic abnormality is diagnostic; in others, it is only suggestive. In still other dysplasias, no obvious histologic abnormality can be found. Because of the lack of experience of most morphologists with such growth-plate sections, their processing and evaluation should be done in one of the centers devoted to the study of these diseases. Biochemical studies are of diagnostic value in only a few of the skeletal dysplasias, such as hypophosphatasia, the rachitic disorders and the mucopolysaccharidoses. Various alterations in type I collagen have now been described in cases of osteogenesis imperfecta, and it is likely that similar molecular defects in type II collagen and the proteoglycans will be discovered in other types of skeletal dysplasia in the near future.[48]

Conclusions

The workup of a short patient is a very orderly and logical exercise. A flow chart can be constructed that enables one to approach evaluating for short stature in a stepwise manner, ultimately establishing a diagnosis (Figure 4). First, the two common nonpathologic forms of short stature, familial short stature and constitutional delay, must be excluded by taking into account the family history both with regard to absolute height and the time taken to reach that height. Bone age should be delayed to about the same extent as the height age in constitutional delay, whereas it should be normal for age in familial short stature. In both cases, the children should have no evidence of other disease and IGF levels should be normal.

If pathologic short stature is established, proportionality must be determined. If the shortening is proportionate and a prenatal onset is found, then those disorders within the category of intrauterine growth retardation, such as the dysmorphic syndromes, chromosomal abnormalities, intrauterine infection and maternal exposure to teratogens, must be considered. Chromosome studies are indicated if the child has dysmorphic features or is a girl with an undiagnosed form of proportionate short stature. If the onset of the proportionate dwarfism is postnatal, then endocrine, metabolic, psychiatric and nutritional causes or chronic diseases must be considered. Measuring IGF and thyroid hormone levels may provide a quick screening test, but provocative tests for plasma hGH and study of the IGF and growth response to exogenous hGH may be required to make a diagnosis. If, on the other hand, the initial examination shows disproportionate dwarfism, the child probably has one of the skeletal dysplasias and the

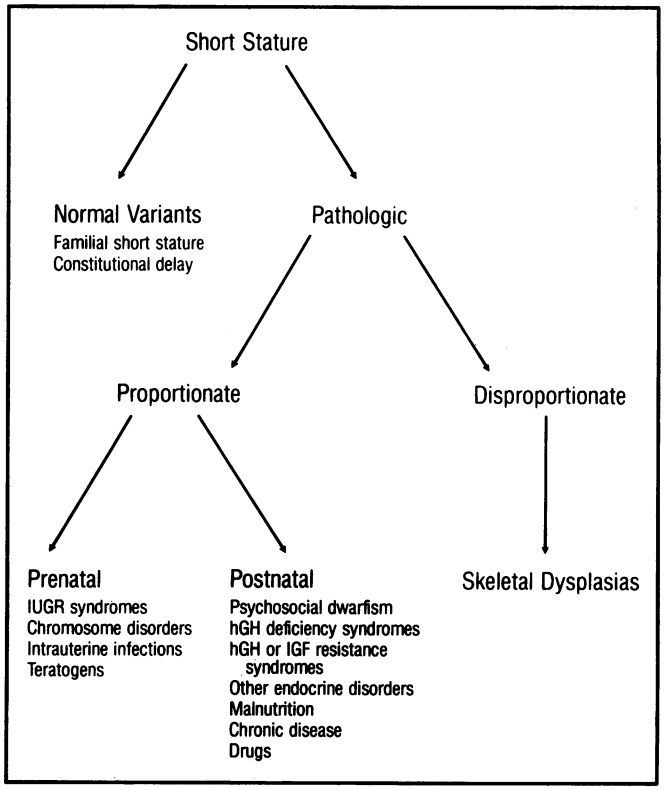

Figure 4.—Differential diagnosis of short stature. hGH = human growth hormone, IGF = insulinlike growth factor, IUGR = intrauterine growth retardation

workup will be considerably different. Careful attention must be paid to the clinical and genetic features, but these diseases have generally been defined on the basis of the radiographic changes and, more recently, histologic features. A full set of skeletal x-ray films will be required and, in some cases also, an iliac crest biopsy to establish the diagnosis.

Once diagnosis is made, the family must be given accurate genetic counseling, prognostic information regarding the complications of the disorder and their treatment or prevention, the possibility or lack of possibility of growth stimulation and, finally, psychological and social counseling regarding the upbringing of a dwarfed child and how to adjust best to the situation. These last problems are frequently best approached by referral to a lay group, such as the Little People of America.

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